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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1634	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,449	ARCOT, SANTOSH S.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group II, claims 10-36 in Paper No.9 is acknowledged. The traversal is on the ground(s) that: (1) "Groups I and II are related inventions and do not require different and distinct searches and, thus, examination of both groups will not be unduly burdensome." since "the assays of Group I are generic to the assays of Group II." according to the definition of "bound probe"; and (2) "both invention groups are classified in the same class and subclass: class 435, subclass 6, the inventions do not have separate classification."

After carefully considered applicant's arguments, applicant agreed to withdraw the restriction requirement and combine Groups I and II together. Therefore, claims 1-36 will be examined.

Specification

2. The disclosure is objected to because of the following informalities: (1) there are a lot of nucleic acid sequences in the specification without SEQ ID NOs; (2) in page 21, last paragraph bridging to page 22, first paragraph of the specification, there are detailed description of Figure 6. Some description is related to PCR primer S1 and biotin molecule R1. However, there is no S1 and R1 in Figure 6; and (3) " 95 C" in line 12 of page 22 should be "95 ^{0}C". The examiner find that similar errors distribute in whole specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Note that claims 2-9 are dependent on claim 1, claims 11-29, 35, and 36 are dependent on claim 10, and claims 31-34 are dependent on claim 30.

5. Claim 1 is rejected as vague and indefinite in view of the phrase "at least one of detecting the presence of the spectrally addressable ligated products or analyzing the nucleic acid sequence of the spectrally-addressable ligated products" because it is unclear what it intended. "at least one" in the phrase needs to be deleted in order to understand the phrase. For example, does this phrase mean detecting the presence of the spectrally addressable ligated products or analyzing the nucleic acid sequence of the spectrally-addressable ligated products or this phrase mean something else? Please clarify.

6. Claim 5 is rejected as vague and indefinite in view of the phrase "the sample is contacted with two subsets of free probes and one subset of spectrally-addressable bound probes, wherein the first subset of free probes is specific for the first portion of the one or more first target nucleic acid sequences and the second set of spectrally-addressable bound probes is specific for the first portion of the one or more second target nucleic acid sequences" because it is unclear what it intended. According to the first part of this phrase, the sample is contacted with two subsets of free probes and one subset of spectrally-addressable bound probes, it is unclear where the second

set of spectrally-addressable bound probes in the second part of the phrase comes from and the first part of the phrase does not appear to correspond to the second part of the phrase. Please clarify.

7. Claim 8 is rejected as vague and indefinite because it is unclear how the relative amount of fluorescence dye incorporated into the spectrally-addressable bound probes can be used to distinguish different bound probes. Note that, since a substantially same amount of fluorescent dye is incorporated into each bound probe, the relative amount of fluorescence dye incorporated into the spectrally-addressable bound probes must be the same. Please clarify.

8. Claim 10 is rejected as vague and indefinite in view of the phrases "at least one subset of microspheres to which are coupled bound probes" and "coupling a bound probe to a microsphere", and steps (b) and (c) of the claim because it is unclear what it intended if the examiner compares the definition of "bound probe" in the specification (see page 9), Figures 1 and 6, and applicant's arguments in page 3, second paragraph of applicant's remarks with above phrases in this claim. According to the definition of "bound probe" and applicant's arguments, bound probe is "a probe which is bound to a solid support, and in which the solid support is labeled for detection". In other word, bound probe is a probe that is attached a labeled solid support. Since the solid support can be particle, 5' and 3' of the bound probe in steps (b) and (c) appear to have attached particle, in the examiner's opinion, it is impossible that such bound probe can ligate with free probe because both ends of bound probe have been blocked by the particles. Furthermore, according to Figures 1 and 6, no such bound probe is taught by the specification. Please clarify.

9. Claim 10 is rejected as vague and indefinite in view of the phrase "the bound probes of a given subset of microspheres" because it is unclear since microsphere does not include bound probes. Please clarify.

10. Claims 13 and 14 are rejected as vague and indefinite because it is unclear what it intended. Since the bases in a nucleic acid probe are connected by phosphodiester bonds, both ends of a nucleic acid contain phosphates. It is unclear what mean that "the free probe further comprising a phosphate at the other of their end". Does this phrase mean that the free probe further comprising a phosphate label at the other of their end or this phrase mean something else? Please clarify.

11. Claim 16 is rejected as vague and indefinite because it is unclear what it intended. Does the phrase " the bound probes differ in that the nucleotide found at one end of one subset differs from that found at the corresponding end of the other subset" mean that the nucleotide sequences at one end of one subset of bound probes are different from the nucleotide sequences at one end of another subset of bound probes or this phrase mean something else? Does the phrase "wherein the nucleotide sequences comprising the at least two subsets of bound probes are otherwise substantially identical" mean that the nucleotide sequences at one end of one subset of bound probes are substantially identical to the nucleotide sequences at one end of another subset of bound probes or this phrase mean something else? Please clarify.

12. Claim 20 is rejected as vague and indefinite because it is unclear what it intended. The phrase "the nucleotide and the detectable label found at opposite ends of one set differing from that nucleotide and the detectable label found in the corresponding ends of the other set" is

unclear because, from claim language of this phrase, it is unclear whether free probes have one detectable label or two detectable labels. Does this phrase mean the nucleotide sequences at opposite ends of one set differing from that nucleotide sequences in the corresponding ends of the other set or this phrase mean something else? Please clarify.

13. Claim 20 is rejected as vague and indefinite because it is unclear what it intended. The phrase "wherein the nucleotide sequences comprising the at least two sets of free probes are otherwise substantially identical" is unclear because it is difficult to understand how the nucleotide sequences comprising the at least two sets of free probes can be considered to be substantially identical if nucleotide sequences and detectable labels in two sets of free probes are different in one end of the probes. Please clarify.

14. Claim 22 is rejected as vague and indefinite because it is unclear what it intended. The phrase "the oligonucleotides of the at least one set of free probes and at least one subset of microsphere have 5' and 3' ends" is unclear because microsphere itself can not include an oligonucleotide and does not have 5' and 3' ends. Please clarify.

15. Claim 22 is rejected as vague and indefinite because it is unclear what it intended. The phrase "the free probes of a given set include a phosphate at their 5' end" is unclear. Since the bases in a nucleic acid probe are connected by phosphodiester bonds and both ends of a nucleic acid contain phosphates, it is unclear which phosphate can be considered as a phosphate at their 5' end. Does 5' phosphate means a phosphate label or mean something else? Please clarify.

16. Claim 22 is rejected as vague and indefinite because it is unclear what it intended. The phrase "the modifier moiety is an amine which couples the 5' end of the oligonucleotide of the

bound probe to a carboxylic acid group on the microsphere" is unclear. According to the definition of "bound probe" and applicant's arguments, bound probe is " a probe which is bound to a solid support, and in which the solid support is labeled for detection". In other word, bound probe is a probe that is attached a labeled solid support. Since the solid support can be particle, 5' and 3' of the bound probe in the claim appear to have attached particles, in the examiner's opinion, it is impossible that such bound probe can ligate with free probe because both ends of bound probe have been blocked by the particles. Furthermore, according to Figures 1 and 6, no such bound probe is taught by the specification. Please clarify.

17. Claim 23 is rejected as vague and indefinite because it is unclear what it intended. According to the definition of "bound probe" and applicant's arguments, bound probe is " a probe which is bound to a solid support, and in which the solid support is labeled for detection". In other word, bound probe is a probe that is attached a labeled solid support. Since the solid support can be particle, 5' and 3' of the bound probe in the claim appear to have attached particles, in the examiner's opinion, it is impossible that such bound probe can ligate with free probe because both ends of bound probe have been blocked by the particles. Furthermore, according to Figures 1 and 6, no such bound probe is taught by the specification. Please clarify.

18. Claim 23 is rejected as vague and indefinite in view of the phrase " a portion of the oligonucleotide at the 3' end of one subset differs from the a portion of the oligonucleotide at the 3' end of the other subset" because it is unclear what it intended since the subset can not have 3' end. Please clarify.

19. Claim 23 is rejected as vague and indefinite because it is unclear what it intended. The phrase "wherein the nucleotide sequences comprising the at least two sets of bound probes are otherwise substantially identical" is unclear because it is difficult to understand how the nucleotide sequences comprising the at least two sets of bound probes can be considered to be substantially identical. Note that, as shown in the claim, a portion of the oligonucleotide sequences of two bound probes are different. Please clarify.

20. Claim 24 is rejected as vague and indefinite because it is unclear what it intended. The phrase "wherein the nucleotide sequences comprising the at least two sets of free probes are otherwise substantially identical" is unclear because it is difficult to understand how the nucleotide sequences comprising the at least two sets of free probes can be considered to be substantially identical. Note that, as shown in the claim, a portion of 5' end of the probes are different. Please clarify.

21. Claim 25 is rejected as vague and indefinite in view of the phrase "substantially the same reaction vessel" because it is unclear that this phrase mean the same reaction vessel or different reaction vessels. Please clarify.

22. Claim 27 is rejected as vague and indefinite because it is unclear what it intended because the concentration of a fluorescent dye on the microspheres can not used to distinguish fluorescence-labeled microspheres since the concentration means amount per unit. The examiner suggest that applicant replace "concentration" with "amount". Please clarify.

23. Claim 27 is rejected as vague and indefinite in view of the phrase " the microspheres of one subset can be distinguished from the microspheres of the other subset" because the word

"can" in the phrase represent an ability of the microspheres. Thus, claim 27 can not be considered as a method step.

24. Claim 28 is rejected as vague and indefinite in view of the phrase " the spectrally addressable microspheres of one subset can be distinguished from the spectrally addressable microspheres of another subset" because the word "can" in the phrase represent an ability of the microspheres. Thus, claim 28 can not be considered as a method step.

25. Claim 30 is rejected as vague and indefinite because it is unclear how to interpret the phrase "bound probes coupled to spectrally addressable microspheres " in the claim. According to the definition of "bound probe" and applicant's arguments, bound probe is " a probe which is bound to a solid support, and in which the solid support is labeled for detection". In other word, bound probe is a probe that is attached a labeled solid support. Since the solid support can be particle, 5' and 3' of the bound probe in the claim appear to have attached particles. However, according to Figures 1 and 6, no such bound probe is taught by the specification. Please clarify.

Claim Rejections - 35 USC § 102

26. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

27. Claims 1, 2, 4, 7, and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Chee *et al.,* (US Patent No. 6,355,431, priority date: April 20, 1999).

Chee *et al.,* teach detection of nucleic acid amplification reaction using bead arrays.

Regarding claims 1 and 9 , Figures 7A, 7B, 7C, 7D, 7E and 7F showed a method of OLA/RCA (the oligonucleotide ligation assay/rolling circle amplification). First, a first OLA primer 45 bound to microsphere 10 was hybridized with a target sequence 25 and a second OLA primer 50. Following the addition of ligase, the first and second OLA primers were ligated to form a ligated oligonucleotide 56 (modified primer nucleic acid). Following denaturation to remove the target nucleic acid, the immobilized ligated oligonucleotide was distributed on an array. The immobilized ligated oligonucleotide (modified primer nucleic acid) was detected or was used in RCA wherein an RCA probe 57 and polymerase were added to the array resulting in amplification of the circular RCA probe 58 as recited in claim 9. The modified primer comprised a detectable label, such as a fluorescent label, which was either incorporated by the enzyme or present on the original primer (see columns 3-7, 11, and 44 and claims 1-13 in columns 59-61). Note that the first OLA primer 45 was considered as a spectrally-addressable bound probe while the second OLA primer 50 was considered as a free probe.

Regarding claim 2 , Chee *et al.,* also taught to the method comprises hybridizing at least a first primer nucleic acid to a first target sequence to form a first hybridization complex, and hybridizing at least a second primer nucleic acid to a second target sequence that was substantially

complementary to the first target sequence to form a second hybridization complex (see column 4). Since the second target sequence was substantially complementary to the first target sequence, the sequence of the first primer nucleic acid must be different from that of the second primer nucleic acid. Since these first and second primers could attach to microspheres (see Figures 7A, 7B, 7C, 7D, 7E and 7F), they were considered as bound probes that were distinguishable from each other at least based on the nucleotide sequence at the free end of the probes (for the definition of "free end", see page 10 of the specification).

Regarding claim 4, Chee *et al.,* taught the third primer hybridized to a second adjacent domain of the first target nucleic acid while the fourth primer hybridized to a second adjacent domain of the second target nucleic acid (see column 60). Since the second target sequence was substantially complementary to the first target sequence, the sequence of the third primer nucleic acid must be different from that of the fourth primer nucleic acid. Since the third and fourth primer nucleic acids were considered as free probes here, one subset of free probes (the third primer nucleic acid) were distinguishable from other subsets of free probes (the fourth primer nucleic acid) at least based on the nucleotide sequence at the free end of the probes (for the definition of " free end", see page 10 of the specification).

Regarding claim 7, the ligase used in OLA was considered as a thermostable ligase since the ligation reaction was performed in a certain temperature in order to maximize the activity of the ligase.

Therefore, Chee *et al.,* teach all limitations recited in claims 1, 2, 4, 7, and 9.

Claim Rejections - 35 USC § 103

28. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

29. Claims 30-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chee *et al.*, (April 20, 1999) as applied to claims 1, 2, 4, 7, and 9 above.

Regarding claims 30-34, as mentioned in the rejection under 35 USC § 112, second paragraph, it was unclear how to interpret the phrase "bound probes coupled to spectrally addressable microspheres " in the claim because the definition of "bound probe" in the specification, Figures 1 and 6 and the phrase "bound probes coupled to spectrally addressable microspheres" did not correspond each other. Based on the definition of "bound probe" in the specification, and Figures 1 and 6, now the examiner alternatively considered "bound probes coupled to spectrally addressable microspheres" as a nucleic acid probe coupled to spectrally addressable microspheres in this rejection. Chee *et al.*, taught the composition in kit claims 30-34 (see the rejection for claims 1 and 2, columns 5 and 62) and a kit.

Chee *et al.*, did not teach to combine the composition in kit claims 30-34 in to a kit.

However, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have organized the composition recited in claims 30-34 taught by Chee *et al.*, into a kit in view of the patent of Chee

et al., because the kit format was utilized to not only assemble a variety of different reagents together but ensure the quality and compatibility of the reagents. One having ordinary skill in the art at the time the invention was made would have been motivated to assemble reagent (s) of biotechnology methods into a kit in order to obtain the above discussed advantages, thus resulting in instant kit described in claims 30-34. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to assemble a kit as recited in claims 30-34 because the kit could provide a convenient, efficient, economical way to practice the method of Chee *et al.*.

Conclusion

30. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Faruqi, US Patent No. 6,368,801, filed on April 12, 2000.

31. No claim is allowed.

32. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
October 31, 2002

ETHAN C. WHISENANT
PRIMARY EXAMINER